Exhibit F

#41 attached

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Gordon et al. Examiner: J. Chambers

Serial No: 07/938,322 Group Art Unit: 1804

Filed: August 31, 1992 Attorney Docket: IGI-017

Title: TRANSGENIC ANIMALS SECRETING DESIRED PROTEINS INTO MILK

VIA HAND DELIVERY

Honorable Commissioner of
Patent and Trademarks
Washington, DC 20231

THIRD DECLARATION UNDER 37 CFR 1.132 OF KATHERINE GORDON

1. I hold a Ph.D. degree in Biology from Wesleyan University, and I have worked in the field of molecular biology and gene expression for approximately fifteen (15) years. Currently, I am President and C.E.O. of Apollo Genetics, a biotechnology firm involved working in the field of aging. I was previously employed by Integrated Genetics, Inc. of Framingham, Massachusetts from 1984 to 1989, and then with Genzyme, Inc. from 1989 to 1991 after that company acquired Integrated Genetics, the last position being Associate Director. From the beginning its existence

in 1985, I was responsible for the scientific aspects of the transgenic program at Integrated Genetics, and then at Genzyme after the acquisition of Integrated Genetics.

2. I am the co-inventor of the technology claimed in the above-referenced patent application (attached hereto as Appendix A), and I have carefully studied the patent application. This application discloses methods and gene constructs for producing a recombinant protein which is secreted into the milk of a lactating transgenic animal.

3. I have carefully studied those portions of the U.S. Patent Office Actions dated April 19, 1993 and April 7, 1992, which detail the rejection of the pending claims under 35 U.S.C. §112, first paragraph (at pages 2-4 of the April 19, 1993 Office Action, and pages 2-4 of the April 7, 1992 Office Action, which are attached hereto as Appendices B and C, respectively). I understand that the Examiner has held the specification as not enabling for DNA sequences other than those comprising a whey acid protein promoter, arguing that there is insufficient evidence in the specification to indicate that all milk protein promoters can be used with success for the expression of heterologous polypeptide in a transgenic mammal without undue experimentation. I respectfully disagree.

4. The ability to manipulate the germline of animals to create transgenic species offers a number of opportunities. The above-referenced patent application focuses on the use of transgenic animals for the production of recombinant proteins, particularly human biomedical proteins. The approach of the present application is to target expression to the mammary gland and produce the desired protein in milk. Livestock, including sheep, goats, cows and pigs, synthesize and secrete large amounts of protein in their milk during lactation. Using the DNA constructs disclosed in the present application, this synthetic capacity can be harnessed to offer an alternative to conventional fermentation-scale mammalian cell culture.

5. As pointed out in the present application in the section entitled "Background of the Invention", in many instances it has been possible to utilize the promoter and associated regulatory segments from one gene to control transcription of the coding sequence from another and obtain specific expression of a recombinant protein in tissues appropriate to the regulatory sequences. The ability of promoter sequences derived from the pancreatic elastase, insulin, metallothionein, and α-crystallin genes to drive, in transgenic animals, the precise tissue-specific expression of unrelated coding sequences is particularly striking. See, for example, Palmiter et al. (1982) Nature 300:611; Ornitz et al. (1985) Nature 313:600; Swift et al. (1985) Cell 38 (39; Hanahan, D. (1985) Nature 315: 115; and Overbeek et al. (1985) Proc. Nat'l Acad. Sci. 82: 7815.

6. When expression of a particular set of dispersed genes must be coordinately controlled, it would generally be expected that similar regulatory mechanism direct expression at each locus. For example, synthesis and secretion of many milk proteins is specific to the lactating mammary gland, and expression of the corresponding genes is a developmentally and hormonally regulated process modulated by steroid and peptide hormones. Prior to 1986, it was already widely accepted that one dominant mechanism for controlling gene expression comprised control at the stage of transcriptional initiation, that is, by the interaction of RNA polymerase with transcriptional regulatory elements, such as promoter/enhancer sequences, and other transcriptional factors which form complexes with the regulatory elements. In fact, at the time this invention was made, many genes encoding milk proteins had been cloned, and transcriptional regulatory sequences involved in their expression identified and at least partially characterized. It was generally understood that milk protein genes might share one or more regulatory elements conferring mammary specific and hormone controlled expression. For example, sequence homologies between portions of the 5' flanking sequences of various genes encoding proteins constitutively expressed in milk had been noted.

7. There existed at that time a long pedigree of experimental data indicating that regulatory sequences which control the expression of a particular protein could also be used to control expression of completely unrelated proteins through the construction of hybrid genes. Given that such transcriptional control had in fact been demonstrated in transgenic animals, and that the milk proteins coordinately expressed in lactating mammary epithelia were presumed to share similar regulatory mechanisms for expression, one skilled in the art, at the time the invention was made and in light of the disclosure made in the present patent application, would have reasonably expected that transcriptional regulatory sequences derived from other members of the class of milk serum proteins would function within in the same or similar manner as the WAP regulatory sequences in the claimed method.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code and that such willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Katherine Gordon

Dated: October 4 1993

Signature: